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Information for Physicians

Prenatal Diethylstilbestrol (DES) Exposure: Recommendations of the Diethylstilbestrol-Adenosis (DESAD) Project for the Identification and Management of Exposed Individuals

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Prenatal Diethylstilbestrol (DES) Exposure: Recommendations of the Diethylstilbestrol-Adenosis (DESAD) Project for the Identification and Management of Exposed Individuals

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The DESAD Project is supported by contracts from the Division of Cancer Control and Rehabilitation of the National Cancer Institute, Contracts CN45092, CN45122, CN45124, and CN45157

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NIH Publication No. 80-2049
October 1980

This pamphlet was prepared by the Diethylstilbestrol Adenosis (DESAD) Project, which was funded by the Division of Cancer Control and Rehabilitation, National Cancer Institute, in 1974, to study the frequency and natural history of genital tract changes in women exposed prenatally to diethylstilbestrol (DES). The purpose of this brochure is to update the medical community with current information on the health status of DES-exposed persons, methods available for their identification, and plans for continuing examination and management.

Population at Risk and Conditions Found

It is estimated that up to six million persons—mothers, daughters, and sons—were exposed to DES during its use for high risk pregnancy between 1940 and 1971. The most widespread use of DES during pregnancy was probably between 1946 and 1960. However, its administration continued between then and 1971, when the association between intrauterine exposure to DES and the rare development of vaginal and cervical clear cell adenocarcinoma was described (4).

The risk of development of clear cell cancer is estimated to be no more than 1.4 per 1,000 and possibly as few as 1.4 per 10,000 exposed daughters (8). By 1979, approximately 400 cases of this form of cancer were reported to the Registry for Research on Hormonal Transplacental Carcinogenesis (address on page 26 and 27) from various parts of the world. Approximately two-thirds of these tumors were associated with intrauterine exposure to the nonsteroidal synthetic estrogen, DES, and less frequently to the chemically related synthetic estrogens, dienestrol and hexestrol (see Appendix A). Illustrations of these tumors are presented in the Appendix and in the forthcoming Atlas entitled: "Findings in the Human Female After Intrauterine Exposure to Diethylstilbestrol," (Dept. DES, Office of Cancer Communications, National Cancer Institute, Bethesda, MD 20205).

Noncancerous changes appear in the vagina in about one-third and in the cervix in nearly every DES-exposed daughter (2,3). The most common changes, including gross structural changes of the vagina and cervix and adenosis (glandular epithelium or its secretory products) of the vagina, are illustrated in Appendix B of this pamphlet. Less frequently observed changes are presented in the Atlas.

The speculation that squamous cell dysplasia would develop in the vagina or cervix in a large percentage of exposed daughters has received no support from the recent report of the DESAD project (2,3), which suggests that at this time dysplasia may be no more common in DES-exposed daughters than in the unexposed population.

Recent studies have indicated that DES-exposed women may be at an increased risk for late pregnancy loss. In some exposed daughters the uterine corpus may vary in size and shape, but the functional significance of this observation is still unknown (28,38).

Limited studies in males have shown no association between in utero DES exposure and cancer of the genitourinary tract (21,27). However, nonneoplastic changes including epididymal cysts and hypoplasia of the testis have been described.

Mothers of the DES-exposed daughters are also being studied. Although one study reported a slightly higher frequency of breast cancers in exposed mothers (4.6 percent) than in non-exposed mothers (3.1 percent), this difference is not statistically significant based on the small number of women studied. Further study and continued surveillance of mothers, however, are continuing (18).

Identification

Many mothers and their children do not know whether or not they were exposed to DES. Ideally DES-exposed individuals are identified by physicians' review of their complete obstetrical records. This method can identify mothers who have forgotten that they received DES or daughters for whom no changes are found by gynecologic examination. However, this method is not always practical. In many cases old records have been destroyed, and hospital obstetrical records do not always mention antenatal medications. Even if such information is available, the mothers of exposed children cannot always be located.

A more practical method to alert individuals about DES is for health care providers to display educational materials in their waiting rooms. Since a history of DES exposure may not be volunteered, relevant questions should be included in the medical histories. Questions which might elicit a DES history include: Did you or your mother take DES during pregnancy? Have problems carrying a pregnancy to term? A history of miscarriages or threatened miscarriage? Vaginal bleeding in pregnancy?

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records wherever possible.

In the event that the mothers, daughters and sons are unaware of exposure, a health care provider may still be able to suspect DES exposure in daughters based on the gross findings observed at examination and illustrated in Appendix B. These daughters should be followed in the same manner as women with known exposure.

Examination and Referral of Daughters

The examination of a DES-exposed female is, with some amplification, similar to a routine pelvic examination. The gynecologic examination used in the DESAD Project to examine DES-exposed daughters is outlined in the table below. Additional techniques found useful in performing the examination are described. When changes characteristic of the DES-exposed populations are present, the physician may wish to consult a gynecologist familiar with the details of evaluation and followup of DES-exposed individuals.

Order of Gynecologic Portion of Examination of Women Exposed to DES in Utero (see figures 1-8)

Vulvar Inspection

Vaginal and Cervical Palpation (Digital)

Vaginal and Cervical Inspection (Speculum)

Cytology (Separate Slides of Vaginal Fornices and Cervix)

Colposcopy (Optional)

Iodine Stain of Cervix and Vagina

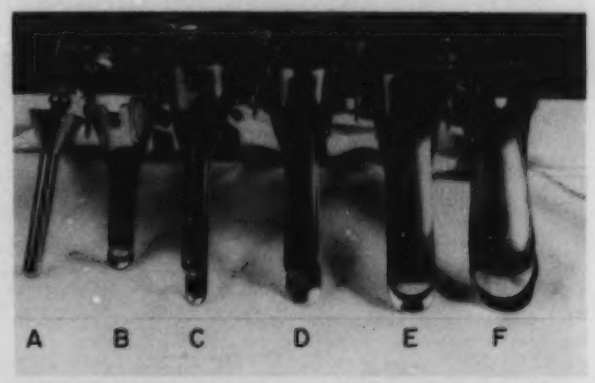
Tissue Biopsy of Atypical Findings

Bimanual (Recto-vaginal) Examination

the hymen is unusually tight, a topical anesthetic jelly or spray may reduce discomfort during the initial stages of dilation. If the hymen permits the passage of the index finger, the examination may proceed. The patient should be encouraged to use tampons during menstrual periods as this will facilitate the initial and future examinations.

Palpation of the Vagina Palpation is a crucial part of the DES examination and may provide the only evidence of clear cell adenocarcinoma, especially on the rare occasion when it is located beneath the mucosa. The finger used for palpation should be moistened with water rather than lubricant jelly in order not to ruin the cytologic specimens obtained subsequently. The entire length of the vagina including the fornices should be carefully assessed. During palpation vaginal ridges and structural changes of the cervix may be noted. Areas of thickening or induration should arouse suspicion and be sampled by biopsy.

Speculum Examination After palpation, a speculum of appropriate size is inserted (figure 1). In virginal females the Pederson virginal speculum is frequently effective when the standard virginal speculum is too short to permit examination of the entire length of the vagina as



A. PEDIATRIC RECTAL SPECULA
B. VIRGINAL SPECULUM
C. VIRGINAL SPECULUM
D. PEDERSON SPECULUM, NARROW
E. PEDERSON SPECULUM
F. GRAVES SPECULUM

Figure 1 Vaginal specula (By permission of Barnes AB: Ambulatory Management of the DES-Exposed Patient[14]).

well as the fornices. Warm water, not jelly, should be used for lubrication during insertion of the speculum. Excess mucus, sometimes present in the DES-exposed woman, should be gently removed with a moist cotton swab. The epithelial surface of the vagina must be carefully inspected. Grossly, adenosis may appear red and granular, while squamous metaplasia may be indistinguishable from normal squamous epithelium. During the course of gross inspection, the speculum should be gently rotated as it is withdrawn in order to assess properly the entire length of the vagina.

Cytology The secretions and epithelium in the upper third of the vagina should be thoroughly sampled with a wood or plastic spatula, as should the middle or lower third of the vagina if gross epithelial changes are evident there (figure 2).

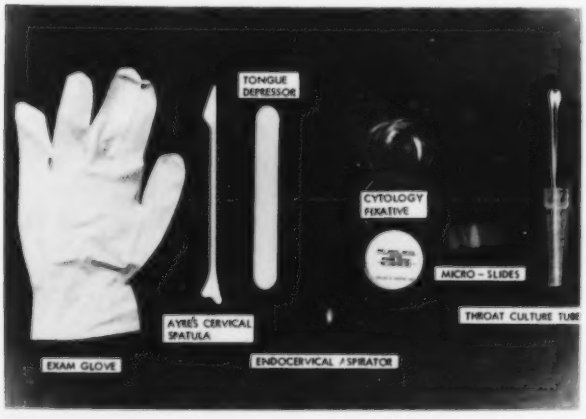


Figure 2 Papanicolaou smear equipment (By permission of Barnes AB: Ambulatory Management of the DES-Exposed Patient[14]).

The spatula should be rotated along the entire circumference of the vaginal fornices. The vaginal material should be promptly transferred to a slide and immediately placed into fixative. A second sample from the cervix should be obtained from the endocervical canal and ectocervix. Aspiration of the external os may be performed as a method for sampling the endocervical canal.

This procedure should be followed by a scrape of the ectocervix. When an abnormal smear is reported, a physician may wish to consult a gynecologist experienced in evaluating DES-exposed daughters.

Colposcopy Colposcopy, if performed, should be done before iodine staining (figure 3). The chief benefits of colposcopy are that it permits an accurate assessment of the extent of epithelial changes on the cervix and vagina and can be used as an aid to detect those areas most likely to disclose abnormalities on biopsy. Colposcopy has not proved to be essential in the detection of clear cell adenocarcinoma. This is due to the lack of specific vascular changes with the clear cell adenocarcinoma and to the fact that some tumors may be confined to an intramural location in the vagina and cervix.

Iodine Staining Iodine staining of the vagina and cervix confirms the boundaries of epithelial changes observed by colposcopy, or indicates the boundaries when colposcopy has not been done (figures 3-5). If colposcopy has been performed,

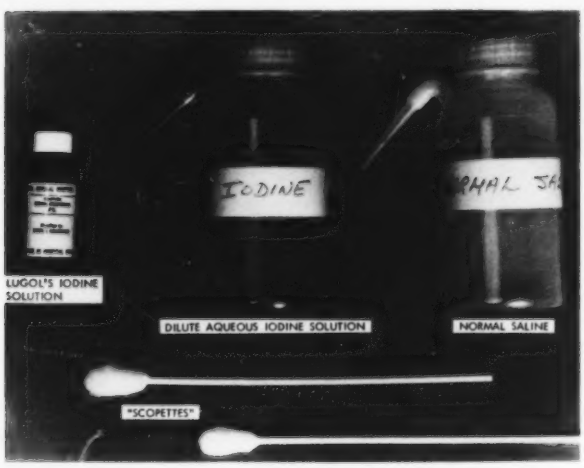
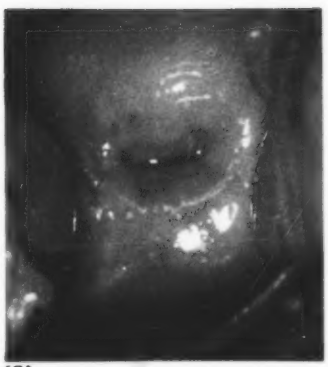


Figure 4 Tissue staining equipment (By permission of Barnes AB: Ambulatory Management of the DES-Exposed Patient[14]).



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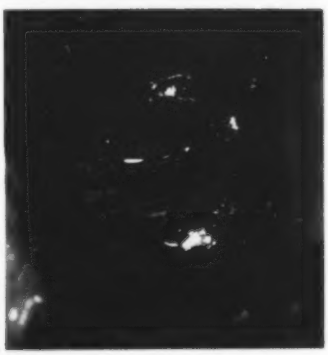

Figure 3 Normal cervix in a DES-exposed woman as viewed through a colposcope. After acetic acid has been applied, normal squamous epithelium is pink (top). After application of an iodine solution, the entire surface of the ectocervix becomes brown because of the high glycogen content of the normal squamous epithelium (bottom).

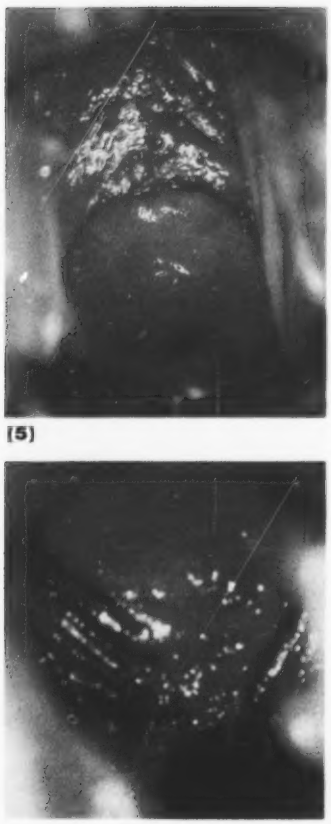

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Figure 5 Iodine staining of cervix and vagina. Prior to application of the stain the mucosa of the cervix and vagina appear homogeneous (top). Afterwards, the entire cervix and portions of the vagina fail to take up the stain and are distinct from those areas of the vagina which stain normally (bottom).

Lugol's solution at half strength is recommended for iodine staining (half strength is 2.5 percent iodine with 5 percent potassium iodide in water). Otherwise Schiller's solution is recommended (1 gram iodine and 2 grams potassium iodide in 300 ml. water). Because the iodine stains only the normal (highly glycogenated) surface epithelium lining the vagina and cervix, this technique cannot be relied upon for detecting lesions within the wall. To properly assess the tissues after staining, the speculum is rotated as it is withdrawn. After inspection, the speculum should be reinserted for biopsy, if indicated. Insertion may be faciliated by lubrication with jelly to compensate for the dehydrating effect of the iodine.

Indications for Biopsy Biopsy should be performed whenever the vagina or cervix is indurated, granular, contains a palpable nodule or larger mass, has discrete areas that appear to be of a different color or texture than the surrounding tissue, or discloses highly atypical colposcopic findings (figures 6-8). Random

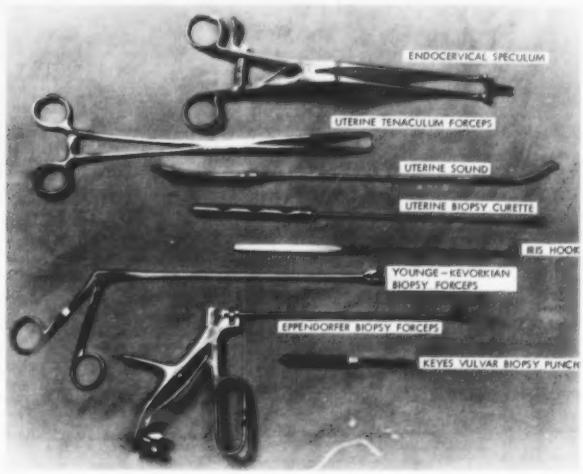


Figure 6 Biopsy instruments (By permission of Barnes AB: Ambulatory Management of the DES-Exposed Patient[14]).

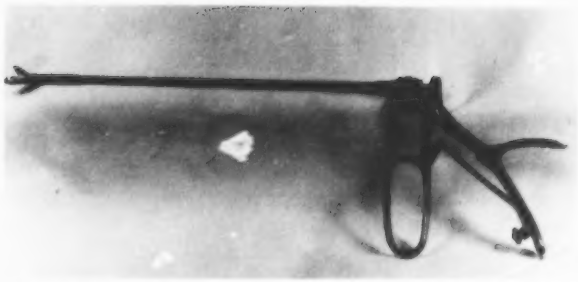


Figure 7 Eppendorfer biopsy forceps (By permission of Barnes AB: Ambulatory Management of the DES-Exposed Patient[14]).

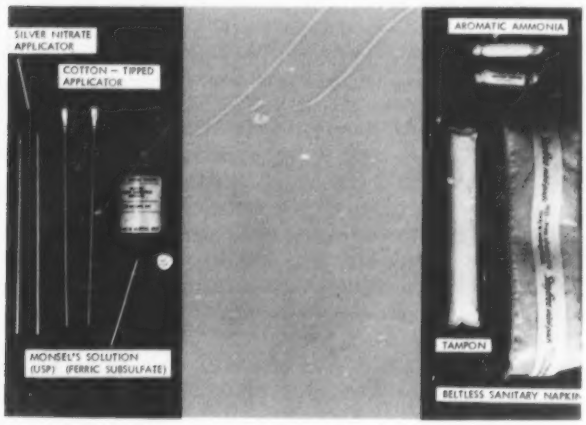


Figure 8 Hemostasis equipment (By permission of Barnes AB: Ambulatory Management of the DES-Exposed Patient[14]).

sampling of nonstaining areas of the vagina or the cervix is not recommended since these areas rarely disclose neoplastic or preneoplastic lesions. Ferrous subsulfate (Monsel's solution), silver nitrate, or Gelfoam with tampons may occasionally be required to stop bleeding after biopsy.

Bimanual Examination The bimanual examination should include examination of the vagina and rectum and should be performed in a routine manner.

Examination Schedule

Initial examination of known or suspected DES-exposed females should be performed after menarche or by the age of 14 years if menarche has not occurred. Examination of younger girls is not advised, unless vaginal bleeding, spotting, or abnormal discharge occurs and then it should be considered mandatory. Hospitalization and examination under anesthesia are rarely necessary.

The interval for followup examination is determined on an individual basis. For most patients with nonstaining epithelial (figure 5) or structural changes (see Appendix B, figures 10-15) in the vagina or cervix or for microscopical changes such as adenosis, yearly examinations are adequate. Patients with abnormal Papanicolaou smears should be referred to a physician experienced in the evaluation of DES-exposed women. Before a diagnosis of dysplasia is considered established, all abnormal cytologic specimens and all biopsy specimens should be reviewed by a pathologist who is thoroughly familiar with the changes in samples from DES-exposed women since immature squamous metaplasia is frequently difficult to distinguish from dysplasia.

Important steps at the followup examination include palpation, inspection, and cytology. Attention should be focused on the changes observed since the initial evaluation. Cervical cytology is presently performed each year. If there are no epithelial changes in the vagina, smears from the vagina can be omitted. Women should be asked about interval bleeding or abnormal discharge.

Education and Counseling

Knowledge of DES exposure without sufficient information and understanding can produce great anxiety. DES-exposed women have anger, guilt and fear about the risk of cancer and concerns about fertility and their sexual self-image. For this reason, it is important that time be allocated at the initial examination for the mother and her daughter to receive complete and accurate information and assurance. Explanations must be given which are appropriate to the age of the patient and in terms she can understand. Educational materials, such as written descriptions of the examination or drawings of the changes associated with DES exposure can be given to the patient when she arrives for her appointment, thus allowing her some time to prepare questions.

Areas of Concern to Exposed Individuals

The following questions reflect areas of concern to the DES-exposed daughter.

Q. What is a daughter's chance that a cancer will develop because of DES exposure?

A. The cumulative risk is between 0.14 percent and 0.014 percent of exposed daughters under the age of 25 years (8). It is unknown if the risk will increase as the daughters become older. While it is important to emphasize the low risk of clear cell adenocarcinoma, the patient's concerns that cancer or additional problems will develop should not be casually dismissed.

Q. Is there a time when daughters will no longer be at risk for clear cell adenocarcinoma?

A. The frequency of this form of cancer appears to be at a maximum at age 19 and is very low by the age of 25 (8). However, it is not known whether these women will ever be risk free since clear cell adenocarcinoma in women not exposed to DES occurs usually during the postmenopause.

Q. Shouldn't vaginal adenosis be treated?

A. Adenosis should only be treated in the unlikely event that it causes symptoms.

Q. Will adenosis develop into cancer?

A. Some DES daughters have had both adenosis and clear cell adenocarcinoma. A progression from adenosis to cancer has not been documented in carefully followed DES daughters although such progression has been suspected in rare cases.

Q. Will adenosis or other changes associated with DES exposure increase in severity over time?

A. Adenosis may disappear spontaneously without therapy. Structural changes of the cervix and vagina, such as illustrated in figures 10-15, may also spontaneously heal and disappear over time (13). An increase in the extent of vaginal adenosis has not been observed.

Q. Will DES-exposed daughters develop dysplasia?

A. Despite earlier predictions that dysplasia might develop in up to about one-sixth of the exposed population (41,63), it was observed in one recent study in only 2.1 percent of exposed women at the time of their initial examination and at the rate of 0.85 percent for the next several years of followup (53). In the DESAD project where the results were based only on the biopsy findings and not the combined results of biopsy and cytologic smears, the rate was somewhat lower (1.1 percent) (2,3). Although these early results suggest that squamous cell dysplasia may be no more common in DES-exposed women than in the general population, it is important that DES-exposed daughters be followed since it is not known if increasing rates may be detected over time.

Q. How should women with dysplasia be treated?

A. Treatment must be planned individually for each woman. Preliminary data indicate that in many instances mild and moderate dysplasia may regress over time without treatment.

Q. Do daughters experience irregular menstrual periods because of DES exposure?

A. Probably not. Preliminary published data from one DESAD center suggests that menstrual irregularity is no more frequent in exposed than unexposed daughters (15). Some DES daughters, like other women, experience menstrual irregularity that may be temporary or continuing.

Q. Do DES-associated changes interfere with sexual intercourse?

A. No.

Q. Does DES exposure alter the ability of daughters to become pregnant and have children?

A. Preliminary data from the DESAD Project indicate that the frequency of conception is no different in exposed and unexposed women.

However, the ability to give birth to a full term, live infant may be impaired. While it is not yet possible to determine whether these findings represent a significant problem, DES-exposed women who are pregnant should be considered at high risk and managed as such. After the twentieth week of gestation, the fetal status should be assessed frequently, probably weekly, including examination for possible cervical dilatation. As additional information becomes available, it may be possible to limit the examinations to specific subgroups of exposed women. No such selection may be made at this time.

Q. Will children of DES-exposed daughters have birth defects or other abnormalities?

A. No evidence is available to suggest that children born of DES daughters will have an increased frequency of birth defects or other abnormalities. Studies in this area are in progress.

Q. Is oral contraceptive usage safe for DES-exposed women?

A. DES-exposed women are not known to have more complications associated with birth control pills than other women. In an occasional woman, microglandular hyperplasia, which is benign and usually related to usage of oral contraceptive medication, will develop in foci of adenosis and must be distinguished from malignant clear cell adenocarcinoma (56).

Q. Are women being exposed to DES today?

A. As of January 1, 1980, the U.S. Food and Drug Administration (FDA) has approved the use of DES for the following purposes (other estrogens are also used for these purposes):

a) Estrogen replacement therapy in young women whose ovaries have been removed or who have retarded growth and sexual development (hypogonadism).

b) Therapy for menopausal symptoms such as hot flashes, night sweats and drying or thinning of the vaginal lining (atrophic genital changes).

c) Treatment of selected cases of advanced cancer of the breast or prostate.

d) Suppression of lactation in new mothers who do not breast feed their infants. The FDA may prohibit this use.

e) The use of DES for osteoporosis is under consideration.

f) The FDA is currently considering the use of DES as a postcoital contraceptive (the so-called "morning after" pill). To the extent that the drug is currently prescribed for this purpose, it is used without proper physician or patient labeling. One of several concerns over the use of DES as a postcoital contraceptive is that some women may already be pregnant from a previous intercourse. The potential offspring of such a pregnancy would be exposed to the risks previously described for DES offspring.

The following questions represent areas of concern to women (mothers) who took DES while pregnant.

Q. Are there any special complications if mothers took DES during pregnancy?

A. None are known.

Q. What followup care should exposed mothers receive?

A. Women who took DES during pregnancy should advise their physicians of this fact. The examination for asymptomatic DES mothers should be that considered appropriate for women of similar ages without prior estrogen exposure, which consists of a regular pelvic examination including a bimanual palpation, Papanicolaou smear and breast examination.

Q. How should a woman examine her breasts? What constitutes a complete breast examination?

A. A free booklet *Breast Self-Examination* is available from the Office of Cancer Communications, Dept. DES, National Cancer Institute, Bethesda, Md 20205.

The following question concerns DES-exposed sons.

Q. Should sons be examined on a routine basis because of exposure to DES?

A. Sons exposed in utero to DES should be informed of the exposure, but a physical examination is not required. No association of DES exposure and subsequent development of cancer in the sons has been described. Matters of possible male infertility are currently under investigation (17,27).

Appendix A

DES-Type Drugs That May Have Been Prescribed to Pregnant Women

Nonsteroidal Estrogens

Benzestrol
Chlorotrianisene
Comestrol
Cyren A.
Cyren B.
Delvinal
DES
DesPlex
Dibestil
Diestryl
Dienestrol
Dienoestrol
Diethylstilbestrol Dipalmitate
Diethylstilbestrol Diphosphate
Diethylstilbestrol Dipropionate
Dithylstilbenediol
Digestil
Domestrol
Estilben
Estrobene
Estrobene DP.
Estrosyn
Fonatol
Gynben
Gyneben
Hexestrol
Hexoestrol
Hi-Bestrol
Menocrin
Meprane
Mestilbol
Methallenestril
Microest
Mikarol
Mikarol forti
Milestrol
Monomestrol
Neo-Oestranol I
Neo-Oestranol II
Nulabort
Oestrogenine
Oestromenin
Oestromon
Orestol
Pabestrol D.
Palestrol
Restrol
Stil-Rol
Stilbal
Stilbestrol
Stilbestronate
Stilbetin
Stilbinol
Stilboestroform
Stilboestrol
Stilboestrol DP.
Stilestrate
Stilpalmitate
Stilphostrol
Stilronate
Stilrone
Stils
Synestrin
Synestrol
Synthoestrin
Tace
Vallestril
Willestrol

Nonsteroidal Estrogen—Androgen Combinations

Amperone
Di-Erone
Estan
Metystil
Teserene
Tylandril
Tylosterone

Nonsteroidal Estrogen—Progesterone Combination

Progravidium

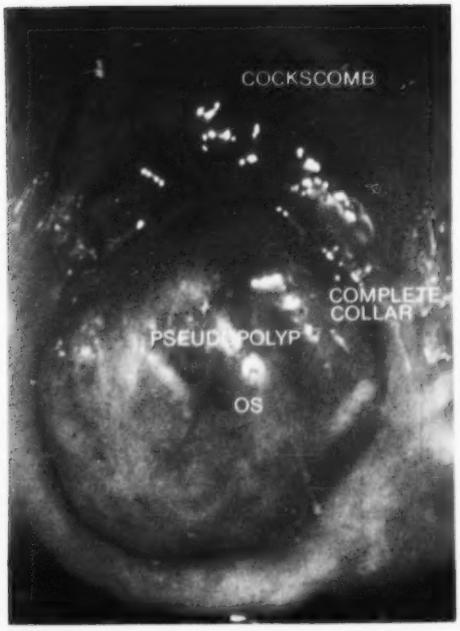
Vaginal Cream—Suppositories with Nonsteroidal Estrogens

AVC cream with Dienestrol
Dienestrol cream

Appendix B

Changes Observed in DES-Exposed Daughters (Figures 9-18)

Figure 9 Radical vaginectomy-hysterectomy specimen with clear-cell adenocarcinoma of vagina (center). Foci of adenosis appear grossly as stippled red zones in vagina. The extensive ectropion of the cervix also is red grossly.



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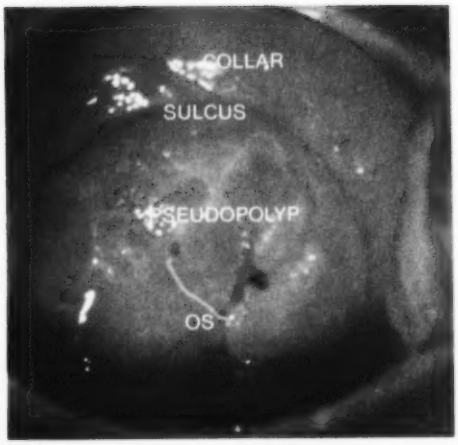

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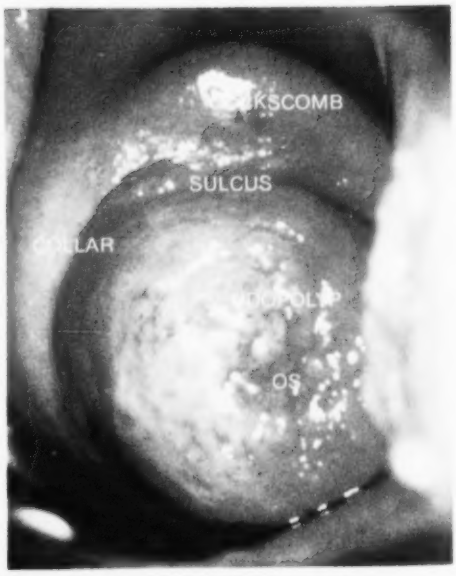

Figure 10 Cockscomb, collars and pseudopolyps of cervix. Cockscomb (hoods) are markedly enlarged folds of cervical stroma and epithelium. Folds that are low and broad are collars (rims). A pseudopolyp is that portion of the cervix medial to a constricting band (sulcus) which has on superficial examination the appearance of a polyp. However the pseudopolyp is not a true polyp since through it traverses the endocervical canal.

Figure 11 Cervical collar that is incomplete and disappears in the area of the anterior cervical lip.

Figure 12 Hypoplastic cervix blending into obliterated vaginal fornix.

(13)

Figure 13 Application of instruments during examination of a DES-exposed daughter. A bulging broad based mass present in the anterior endocervical canal (top) is better seen if a cotton swab is used to lift it and display its borders (bottom).

Figure 14 Colpophotograph of an anterior cervical cockscomb covered with metaplastic squamous epithelium in the pattern of mosaicism and grape-like structures on the anterior cervix that on microscopical examination are lined by glandular epithelium (ectropion).

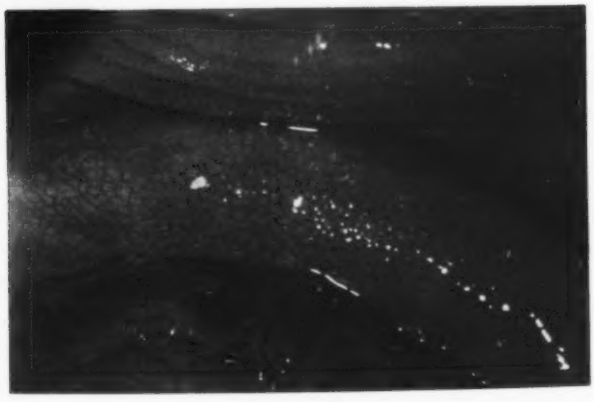

Figure 15 Colpophotograph of an anterior cervical collar covered with metaplastic squamous epithelium in the pattern of mosaicism and ectropion partially replaced with metaplastic squamous epithelium (white patches in lower third of photograph).

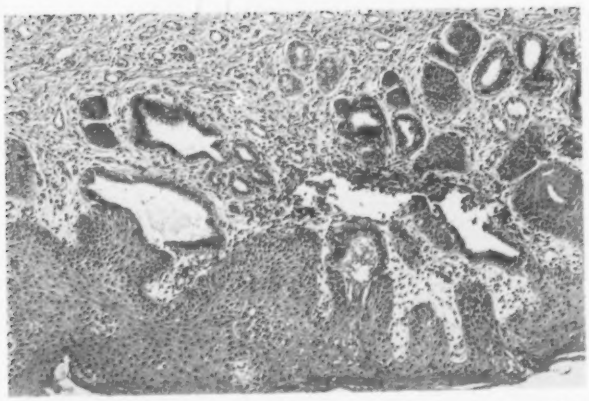

Figure 16 Vaginal adenosis. Glands in the lamina propria lined by tuboendometrial type of epithelium are partly replaced by metaplastic squamous epithelium. The surface epithelium of the vagina is replaced by metaplastic squamous epithelieum which is glycogen poor and therefore does not take up an iodine stain. (H&E x42).

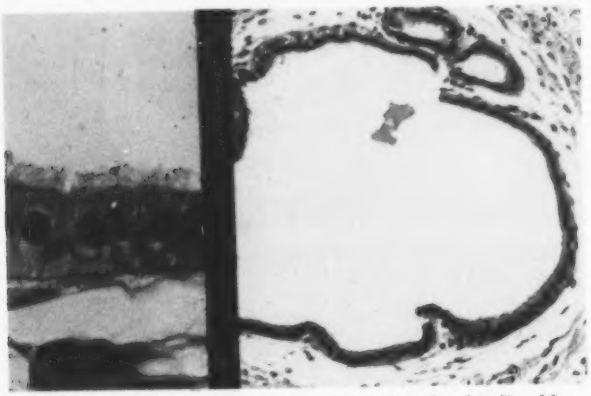

Figure 17 Vaginal adenosis in which the gland is lined by mucinous cells (H&E x 200).

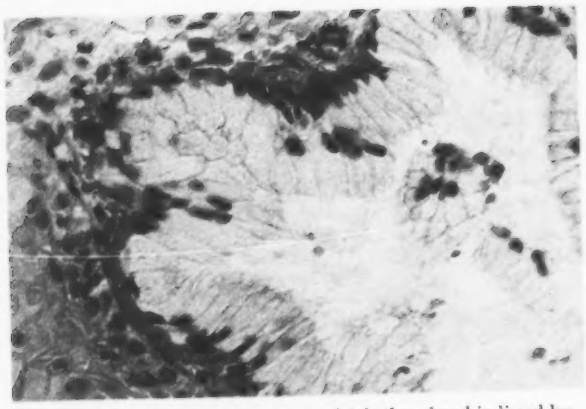

Figure 18 Vaginal adenosis in which the gland is lined by ciliated cells of the tuboendometrial type. (H&E x890).

(no charge, unless indicated otherwise)

Questions and Answers About DES Exposure During Pregnancy and Before Birth. National Cancer Institute, Office of Cancer Communications, Dept. DES, Bethesda, MD 20205.

Breast Self-Examination. National Cancer Institute, Office of Cancer Communications, Dept. DES, National Cancer Institute, Bethesda, MD 20205.

DES Poster. Planned Parenthood of San Francisco, 1660 Bush Street, San Francisco, CA 94109, $2.50 each.

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National Cancer Institute

NIH Publication No. 80-2049
October 1980